EXHIBIT H

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Re: Supplemental Expert Report

I. Introduction

My name is Gerard Sanacora, M.D., Ph.D. I am a psychiatrist and neuropsychopharmacologist at the Yale University School of Medicine. A copy of my current curriculum vitae is appended at Attachment A.

This report contains my opinions as they have developed since the writing of my original expert report and are in response to developments in the Neurontin litigation including the July 10, 2008 FDA Joint Advisory Committee Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and the Psychopharmacologic Drug Advisory Committee as well as plaintiffs' experts' testimony during the Daubert hearing; my opinions are expressed to a reasonable degree of scientific certainty, regarding (1) current scientific understanding of the neurobiological bases of major depression and mood disorders and their symptomatology, including suicidality; (2) the pharmacology of Neurontin (gabapentin) and the commonality and differences that exist in the pharmacodynamics of the group of medications referred to as anti-epileptic drug (AEDs), including whether any scientifically established pharmacological property of Neurontin would support a scientific theory that the compound causes suicide, signals a need for further testing of such a hypothesis, or supports clinical warnings of increased suicide risk; and (3) the significance of the findings of the U.S. Food and Drug Administration's Peripheral and Central Nervous System Drugs and

Psychopharmacologic Drugs Advisory Committee meeting held on July 10, 2008. My opinions on the general issues of the understanding of the neurobiological bases of major depression and mood disorders and their symptomatology, including suicidality; the role of amino acid neurotransmitter systems such as γ-aminobutyric acid (GABA), glutamate, and monoamines in brain and central nervous system function; the pharmacology of gabapentin and other relevant compounds; and the clinical efficacy and safety profile of gabapentin when used to treat human psychiatric and neurological disorders have been set out in my expert report on general medical causation filed in Multi-District Litigation No. 1629, a copy of which is attached as Attachment C and incorporated by reference.

Materials that I reviewed specifically in connection with preparation of this report are listed on Attachment B. References cited specifically within the body of this report are noted bibliographically at the end of the text. My opinions are also based in part upon information gained through my medical and scientific education and training, my professional familiarity with the medical and scientific literature germane to the subject matter, and my discussions with colleagues, my research experience, and my clinical experience. It is not possible to list all of the manuscripts and documents that support or that I consider relevant to my opinions, however, I have listed all of the materials provided to me in specific connection with my work in this matter or that I consider particularly important to the subjects of this report. I will supplement this report to the extent any new scientific developments or additional information warrant its revision.

My major opinions in this matter may be summarized as follows:

1) The neural mechanisms mediating emotion and behavior in humans are extremely complex. Our current understanding of these processes remains insufficient to

reliably predict how emotion and behavior will be affected based solely on a molecule's ability to slightly alter the level or release of one or another neurotransmitter system in isolation or in specific laboratory conditions. Clinical effects of pharmaceutical compounds must be determined in controlled human clinical studies. The fact that a group of compounds commonly share a particular therapeutic effect does not mean that the compounds are identical or simply substitutes for one another in terms of other beneficial or adverse effects. In other words, a clinical effect associated with one chemical compound cannot be imputed across chemically and pharmacologically distinct compounds, even if those compounds happen to share some therapeutic property. Specifically, based on existing scientific knowledge, I find no credible evidence to support the general hypothesis that any medication that simply increases brain-tissue GABA content would be in anyway causative of depressive episodes or suicidality. In fact, to the contrary, there is mounting evidence that medications that increase brain-tissue GABA content are associated with an antidepressant-like response. With respect to Neurontin's pharmacological profile, there is, therefore, no scientific knowledge of its pharmacology that supports a theory that the compound causes depression or suicide, nor any signal that suggests a compelling reason to conduct further testing of any suicide-induction hypothesis. Rather, Neurontin's pharmacology is entirely consistent with the clinical profile, as demonstrated in controlled trials, which evinces no association with increased suicide risk through any mechanism.

2) In reviewing the FDA's Statistical Analysis and Review, Antiepileptic Drugs and Suicidality (May 23, 2008) and the transcript for the FDA's Expert Peripheral and Central Nervous System Drugs and the Psychopharmacologic Drugs Advisory

Committee meeting held on July 10, 2008, it is my opinion that in general there is a signal suggesting that some, but not all, drugs with anti-seizure activity may be associated with increased rates of suicidality, and that the controlled data for other such drugs, including Neurontin, do not support any such signal or association . Although the results of the overall analysis considering 11 drugs with anti-epileptic properties indicates that 0.43% of the patients in drug treatment groups experienced suicidal behavior or ideation versus 0.22% of the patients in placebo groups, corresponding to an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the drug treatment groups who experienced suicidal behavior or ideation than in the placebo treatment groups, there was no evidence that Neurontin was associated with increased levels of suicidality. Furthermore, the comments by FDA and its advisory experts expressed repeatedly that they saw no pharmacological property of the AEDs that provides a biologically plausible basis for the suicide-induction hypothesis. As applied to the claims made about Neurontin in this litigation, the FDA's analysis reinforces the lack of any pharmacological mechanism common to the class of pooled AEDs, or for Neurontin individually, that might plausibly be predictive of increased suicide risk. Absent a biologically plausible mechanism, and given extensive data that shows no signal of any association between the drug and suicidality, I see no compelling scientific rationale for additional or different testing or warnings for Neurontin with respect to suicidality risk.

II. Qualifications

I am an Associate Professor of Psychiatry at Yale University School of Medicine, and Director of the Yale Depression Research Program. I received my Bachelor of Science (B.S.) degree with a double major in Biology and Psychology from the State University of New York (SUNY) at Stony Brook, graduating *magna cum laude*. I then received a Medical Scientist Training Program Scholarship (funded by the National Institutes of Health (NIH)) from SUNY Stony Brook, where I obtained my Ph.D. degree in Physiology and Biophysics in 1992 and my M.D. degree in 1994.

I completed my clinical training in the residency program in the Department of Psychiatry at Yale University School of Medicine within the specialized NIH funded Neuroscience Research Training Program. My first year of medical internship experience was completed at Yale-New Haven Hospital in New Haven CT. The remainder of the residency was in the Department of Psychiatry at Yale. I then remained at Yale School of Medicine as a post-doctoral fellow for one additional year in the NIH funded Neuroimaging Scientist Training Fellowship.

I have significant clinical and research experience in the fields of Biological Psychiatry and Neuropsychopharmacology. I have been the Director of the Yale Depression Research Program since 2000. This program focuses on using clinical and translational neuroscience studies to advance our understanding of the neurobiological underpinnings of mood disorders and the mechanisms of antidepressant action. I have published more than 50 scientific papers and book chapters related to the neurobiology of depression, several of which are directly related to the relationships of the amino acid neurotransmitter systems, GABA and glutamate, to mood disorders and their treatment

and the use of magnetic resonance spectroscopy (MRS) in psychiatry and clinical neuroscience. I am currently a member of the American College of Neuropsychopharmacology (ACNP) and the editorial board of the Journal of Biological Psychiatry. Additional details are listed in my curriculum vitae (Attachment A).

I am being compensated for work on this matter at an hourly rate of $375. I have previously testified in a deposition in the multi-district litigation, but otherwise I have not testified as an expert witness in any other trial, hearing, or deposition within the past four years.

III. The Alleged Relationship Between Gabapentin's Pharmacology and Mood Disorders and Suicide

Plaintiff's expert witnesses Drs. Trimble and Kruszewski assert a simplistic hypothesis that gabapentin-induced increases in brain GABA lead to a decrease in brain serotonin and thus cause a worsening of mood, depression and suicidal ideation. It is important to recognize that, scientifically, their opinions never rise above the level of hypothesis. Their multi-step process "linking" ingestion of Neurontin to suicidality has never been tested and demonstrated to be correct by them or by anyone else.

At every juncture of this hypothetical sequence of events, the plaintiff's expert witnesses either misinterpret data or rely on outdated and unsupported concepts related to the pharmacological action of gabapentin and the pathophysiology of mood disorders and human behavior. I have outlined the support for my claim below by demonstrating that; (A) there is no clear evidence that gabapentin has a significant effect on brain GABA neurotransmission; (B) that brain tissue GABA content is not indicative of GABA neurotransmission, and even if it were, (C) there is no credible evidence to suggest that an increase in brain GABA content would be associated with a worsening of mood or

increased suicidal behavior (if anything there is evidence to suggest that an increase in brain GABA content would be beneficial in treating mood and anxiety disorders); and finally (D) the overly simplistic hypothesis that decreased serotonin neurotransmission in isolation equals increased depression and suicidal behavior is outdated and unsubstantiated.

A. Gabapentin's Effects on GABA Levels and GABA Neurotransmission

The central and peripheral nervous systems (CNS) (the brain, spinal cord, and peripheral nerves) are complex networks of nerve cells (neurons). The CNS functions via cellular structures and natural chemicals that carry electrical signals from nerve to nerve. Neurotransmitter molecules, such as GABA and the monoamines, are the naturally occurring, essential, message-carrying chemicals of the brain and central nervous system. The body naturally synthesizes, uses, and metabolizes neurotransmitters. Neurotransmitters are found, and function, at various locations, including, inside nerve cells (neurons), or in the synaptic spaces between nerve cells, or bound to receptors located on the surface of nerve cells. At the molecular level, neurotransmitters physically move from one location to another; we speak of their being "released" from nerve endings into the synapses, "binding" to receptor sites on adjacent neurons, and "reuptake" (reabsorption) from the synaptic cleft into the nerve cells. It is only when these neurotransmitters are released form the nerve cells into the extracellular space (synaptic cleft), that they are active in transmitting the electrochemical signal. To simply measure the "level" (concentration) of a particular neurotransmitter in a region of the brain, or the entire brain, or the entire body, tells us little or nothing about the *function* or *activity* of the transmitter. To infer *activity* from *brain-tissue levels* would be analogous to trying to

tell whether a car is accelerating or braking by looking at a gauge that shows only the amount of fuel in the tank.

Scientifically, it remains unknown what, if any, clinically significant effects Neurontin (gabapentin) may have on GABAergic neurotransmission. Although Neurontin was originally developed as a GABA analogue (a molecule derived from, or similar to, the GABA molecule's structure), there is actually no credible scientific evidence that Neurontin has a clinically significant impact on GABAergic neurotransmission. Neurontin appears to have little to no affinity for either the $GABA_A$ or $GABA_B$ receptors(1). Although there is a single report by Ng et al.(2) suggesting gabapentin may have a novel pharmacological effect on $GABA_B$ receptor heterodimers expressing the GABA(B1a) and GABA(B1b) receptor subunits, multiple later studies, attempting specifically to replicate Ng and colleagues research, found no such activity (3)(4). Similarly, the inconsistent results obtained in studies examining gabapentin's effects on measures of GABA synthesis, release and breakdown make it very difficult to draw any firm conclusions(1)(5)(6)(7). At present the best evidence suggest the majority, if not all, of gabapentin's effects on neurotransmission are related to its effects on the $\alpha 2\delta$-2 subunits of voltage-gated calcium channels(8). These points are expounded on more thoroughly in my original report and in Dr. Taylor's report.

To date the best evidence suggesting that Neurontin has any effect on any aspect of the GABAergic neurotransmitter system comes from two studies by Petroff and Kuzniecky that used proton magnetic resonance spectroscopy to demonstrate an increase in cortical brain tissue GABA content in subjects taking gabapentin(9)(10). As illustrated in the following section, this increase in total tissue GABA content cannot be used as

evidence that GABA neurotransmission is increased to any clinically significant extent following ingestion of gabapentin.

B. Meaningfulness of Increased Occipital Cortex GABA Content

In order to evaluate the evidence behind Drs. Trimble's and and Kruszewski's argument suggesting a rise in cortical GABA leads to increased suicidal behavior, it is important to understand the meaning and context of the MRS studies they cite as supporting their hypothesis. The elevated GABA levels seen via *in vivo* MRS studies (for example, Petroff et al. (2000), Kuzniecky et al. (2002), reflect *total tissue* GABA. The large majority of this GABA is contained within the cell, where it is inactive and serves no neurotransmission function. Only a miniscule fraction of the total tissue GABA measured by proton MRS is actually functioning as a neurotransmitter at the synapse. The Petroff and Kuzniecky experiments do not provide information related to actual synaptic GABA or GABA neurotransmission. Notably, in at least one study attempting to measure extracellular GABA (GABA outside of the cell that could be active as a neurotransmitter) via microdialysis after gabapentin administration, no effect was found (11).

To put the findings of the Petroff and Kuzniecky studies in context, we should consider the fact that the same MRS method has been used by Harvard and Boston University researchers to demonstrate a 27% increase in brain GABA levels following the practice of yoga (12). The method has also been used by the Yale group (the same site as the Petroff study) to show that occipital cortex GABA levels decrease by 28% in healthy subjects simply sitting in the dark for an hour (13). In sum, the studies by Petroff and Kuzniecky do not provide any credible scientific evidence that gabapentin

significantly increases GABA neurotransmission in any clinically meaningful way. Furthermore, these studies provide absolutely no evidence that an increase in total tissue GABA content is associated with a worsening of mood or an increase in impulsive behavior. If anything, the evidence that exists, presented in the section below, suggests that an increase in brain tissue GABA levels is associated with beneficial effects on mood and anxiety.

C. The Relationship Between GABA and Mood Disorders

The plaintiffs' experts are correct in reporting that there is increasing evidence of GABAergic involvement in the pathophysiology and treatment of mood disorders. That precise relationship has been a focus of my research and of many others' research. However, the evidence suggests that the relationship between GABA and mood disorders is essentially the *opposite* of what Drs. Trimble and Kruszeski suggest it to be. In fact, the overwhelming majority of this evidence suggests that a *reduction* in brain GABA content (not an increase, as they claim) is associated with depression and mood disturbances, and that drugs and treatments that increase brain GABA content actually tend to *alleviate* the symptoms associated with these disorders (not cause or exacerbate them, as they claim). This so called "GABA deficit" hypothesis of mood disorders is supported by several lines of evidence, including (1) animal studies showing stress-related changes in GABAergic function; (2) the ability of GABA agonists and antagonists to modulate behavioral models of depression in rodents; (3) GABAergic effects of standard antidepressant medications; (4) demonstration of GABAergic abnormalities in depressed patients; and (5) evidence of clinical antidepressant efficacy associated with GABAergic drugs. In general, this data suggests depression is associated with a

decreased level of GABAergic neurotransmission. (A. Schatzberg & C. Nemeroff, Textbook of Psychopharmacology 736 (3d ed. 2000).) A more complete and technical discussion may be found in my published review of this subject(14), a copy of which is appended to this report as Attachment D and incorporated by reference, and also discussed in my previous general causation report.

Specifically related to this case, and contrary to Drs. Trimble's and Kruszewski's argument that gabapentin-induced increases in brain GABA levels would be expected to lead to worsening of mood and suicidal behavior, there is clear and consistent evidence demonstrating that a variety of effective *treatments* for mood and anxiety disorders lead to increased brain GABA levels. Several laboratories, including my own, have previously demonstrated these GABA-elevating effects of mood and anxiety therapeutic agents occur in the exact same brain region studied by Drs. Petroff and Kuzniecky that showed GABA elevations following gabapentin treatment (15)(16, 17)(18)(19)(20)(21)(22). There is also some clinical evidence for gabapentin that tends to be consistent with positive effects on depressive or global mood and well-being in particular patient diagnostic categories(23)(24). However, additional data would have to be developed to demonstrate antidepressant action by conventional standards for proof of efficacy. Although this line of reasoning may be as (overly) simple as the monoamine imbalance proposed in previous eras, it highlights the fact that there is absolutely no reliable scientific basis whatsoever to reason that drugs such as gabapentin that *increase* brain GABA content will have, because of their GABA elevating property, depressogenic effects.

In summary, there is now extremely strong evidence to suggest that dysregulation of the GABAergic system is associated with mood disorders. However, the evidence overwhelmingly suggests lower levels (not elevated levels) of GABA in the brain are associated with depression and anxiety. There are also converging lines of evidence suggesting that treatments resulting in an elevation of brain GABA levels are associated with antidepressant and anxiolytic-like responses -- and not a worsening of mood and anxiety as Drs. Trimble and Kruszewski's reports suggest (25)(26)(27)(28)(14). There is no published data that I am aware of that demonstrates that increasing cortical tissue GABA content is associated with a worsening of MDD or suicidal ideation or behavior. Based on this large body of evidence I do not believe it is scientifically rational to predict that a drug that increases cortical GABA levels would be associated with a worsening of mood or an increase in suicidal ideation or behavior. In fact, this evidence has led several scientists to suggest that increasing GABA function could be a target for the development of novel antidepressant treatments (29, 30)(12). Furthermore, there is absolutely no scientific support for the proposition that any brain tissue GABA level elevation observed after administration of gabapentin is associated with, much less causes, depression or suicidality in patients.

D. Current Scientific Knowledge of the Neurobiology of Mood Disorders

As described more fully in my general causation report, we continue to have a very limited understanding of the complex neurobiological underpinnings of human behavior, especially major depressive disorder (MDD) and suicide. The pathophysiology associated with mood disorders and suicidal behavior is much more

complicated than once perceived. The theory that a deficit in brain monoamine transmission is causative of MDD and that drugs that increase monoamine transmission reverse this deficit, and thereby produce an antidepressant-like response, has been studied for decades. While many pharmacotherapies for mood disorders affect one or more monoamine systems, today, more than 50 years after relationships between monoamine systems and depression were first observed, we know that simplistic conceptions of that theory – that is, that an agent that merely "increases" or "decreases" some aspect of monoaminergic function should help or worsen depressive conditions – are incomplete and invalid models of both the disease and its treatment. In our current scientific understanding of the neurobiological basis of depression, neither the production, exacerbation, or remission of clinical depression or its symptoms may be simply inferred or assumed from an alteration of some aspect of monoaminergic function. To highlight this fact, there are now clear examples of effective antidepressant medications that do not serve to increase monoamine neurotransmission, in fact there are examples of drugs that actually appear to enhance serotonin clearance. For example, tianeptine (Stablon, Coaxil, Tatinol), a widely used antidepressant agent in Europe, Asia and Latin America, has been demonstrated to be at least as effective as the selective serotonin reuptake inhibitors in the treatment of Major Depressive Disorder (31), but tianeptine appears to have a completely unique mechanism of action that is believed to include enhancement of serotonin uptake and reduction of synaptic serotonin levels(32)(33).

The current state of scientific understanding is perhaps best demonstrated in the conclusions of a large meta-analytical study that examined all monoamine-depletion

studies performed between 1966 and 2006. (Monoamine depleting agents significantly reduce available monoamines, which is essentially what Drs. Trimble and Kruszewski imply Neurontin does.) After reviewing and performing statistical meta-analysis of the 90 studies in this area the authors concluded that "[a]lthough previously the monoamine systems were considered to be responsible for the development of MDD, the available evidence to date does not support a direct causal relationship with MDD. There is no simple direct correlation of 5-HT or NE levels in the brain and mood"(34). This point is further highlighted by Dr. Steven Stahl in one of the standard textbooks used to teach medical students and residents about psychopharmacology: "So far, there is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no 'real' monoamine deficit." (S.M. Stahl, Essential Psychopharmacology 2000.). This by no means implies that monoaminergic antidepressants (monamine oxidase inhibitors, tricyclics, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, or other modern monoaminergic antidepressants), are not effective, nor that their monoaminergic effects are not relevant to their clinical efficacy. It means that, as a result of advancing scientific knowledge in neuropsychopathology, current scientific understanding of the neurobiology of depression and suicide does not accept oversimplifications represented by propositions such as that "lower serotonin increases depression" or "higher serotonin reduces depression."

In summary, the simplistic concept that merely increasing or decreasing serotonin release, or the release of any other neurotransmitter for that matter, is likely to directly result in depression or depressive-like behaviors such as suicide is inconsistent with current scientific understanding of the neurobiology of mood disorders and behavior in

general. Specifically, to my knowledge there is no scientific knowledge demonstrating that gabapentin administration produces any monoaminergic change that, in turn, produces or should be expected to produce depression or suicidal thoughts or behavior in human subjects. The chain of events outlined by Drs. Trimble and Kruszewski is not supported by scientific reasoning and the available empirical data. Their hypothesis is based on false or flawed assumptions, misinterpretations of data, and outdated models of the neurobiology and psychopharmacology of depression and suicide and treatment of those conditions. The hypothetical sequence of events that they claim leads from ingestion of Neurontin to suicidal acts is not consistent with the scientific evidence, much of which, as outlined above and in my general causation report, tends to contradict one or more steps in their hypothesis, and simply goes ignored by them.

V. FDA Analysis of Anti-Epileptic Drugs and Suicidality

A. Overall evaluation

On July 10th, 2008 the U.S. Food and Drug Administration held a meeting of the Peripheral and Central Nervous System Drugs and the Psychopharmacologic Drugs Advisory Committees to discuss the results of the agency's analysis of a pooled dataset drawn from 11 drugs with antiepileptic properties. The findings of the overall analysis considering all 11 drugs indicated that 0.43% of the patients in drug-treated groups experienced suicidal behavior or ideation versus 0.22% of the patients in placebo groups, corresponding to an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the drug treatment groups who experienced suicidal behavior or ideation than in the placebo treatment groups. It is important to recognize that this effect was only seen when the drugs were included in a pooled analysis. While the findings from this study do suggest

that at least some of the drugs included in the analysis (particularly lamotrigine and topiramate) may be associated with increased rates of suicidality, these data do not provide any evidence that gabapentin itself is associated with increased rates of suicidality.

Most importantly, the rationale for a combined analysis of the 11 drugs in the FDA study is not based on the true pharmacological properties of the various different drugs. The FDA combined the 11 drugs (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide) in their analysis of antiepileptic drugs based solely on the fact that they were all drugs that were either approved for use as treatments for epilepsy or had antiepileptic properties. However, this grouping does not truly represent a unified pharmacological class of drugs with a common mechanism of action. Instead, it represents a group of drugs that share a common indication or a common therapeutic effect. This is analogous to concluding that all drugs that treat congestive heart failure are of a common class of medications despite the fact that we know that their mechanisms of action are in fact quite varied; diuretics (water pills), inotropes (increase the pumping ability of the heart), vasodilators (medications that enlarge the small arteries or arterioles, so the heart has to work less to pump blood through the arteries), beta-blockers (slow down the heart rate and lower blood pressure) and natriuretic peptides (mechanism not completely known, but thought to lower the pressure in the lungs). Similarly, the drugs included in the FDA AED analysis share a common effect of reducing seizure frequency, but their mechanisms of action vary and differ dramatically from one compound to the next.

In an attempt to address this shortcoming in the study design the FDA attempted to subgroup the 11 drugs into various sub-groups based on mechanisms of action, such as sodium channel blocking drugs, GABAergic and GABAmimetic drugs, and carbonic anhydrase inhibitors. (FDA Statistical Analysis and Review at 13 (May 2008).) However there are two major problems with this approach. First, there is no clear consensus on the mechanism of action for these drugs to allow for such a classification, nor any clear definition of what FDA meant by terms such as "GABAergic" or "GABAmimetic." Second, the same drugs were considered in several of the drug classes (zonisamide in two classes, and topiramate in all three). As Dr. Mentari said, the groups were based on a consensus of the medical review team. However, it is widely accepted by the greater neuroscience and neuropsychopharmacology communities that we continue to have a limited understanding of the pathophysiology related to seizure disorders and an even more limited understanding of the mechanism of action related to anticonvulsant drugs. The FDA investigators acknowledged this fact when they recognized that the drug classifications were not unambiguous. They also specifically stated in the advisory board meeting, "... we have to recognize that we don't have any clear mechanistic understanding of the signal." Inclusion of topiramate in all three groups, for example, reflects the difficulty in this classification scheme, as do the compounds categorized as "GABAergic and GABAmimetic," which clearly differ in their respective binding sites and pharmacological mechanisms.

With specific consideration to Neurontin (gabapentin), an individual analysis of placebo controlled gabapentin trials, including totals of more than 2,900 Neurontin-treated subjects and more than 2,000 placebo controls included in the FDA pooled

analysis (FDA Statistical Analysis and Review at 17), failed to show any evidence that gabapentin is associated with an increased risk of suicidal behavior or manifested any "risk difference" compared to placebo. (Ibid. at 24, 26.) In fact, there was no suicidal behavior observed for any of the patients in the gabapentin controlled trials. In considering the sub-analysis of "GABAergic and GABAmimetic" drugs, we need to acknowledge that there are two major flaws that preclude us from drawing any useful conclusions. First, as expounded on above and even more fully in my general report, there is little evidence to suggest that gabapentin actually has any significant pharmacological actions on the GABAergic neurotransmitter system. Second, interpretation of these mechanism related sub-analyses is severely limited by the fact that topiramate, a drug with a disproportionately high representation of adverse events, and that did evince a statistically significant positive association, was included in all classes, including the "GABAmimetic" class. The inclusion of the same drug with a disproportionately high representation of adverse events in all three subgroups renders the analysis of little to no value. If the topiramate data are excluded from the analysis it is very unlikely that the remaining drugs will continue to show an increased rate of suicidality.

At the end of the meeting, the committees agreed with the agency's conclusion that the finding of a signal of increased suicidality risk should be applied to all drugs included in the analyses, and to all AEDs in general, including compounds that were not analyzed by the agency or the committees. The rationale for the extrapolation was that the adverse event was so rare that it was not possible to identify specific drugs or classes of drugs with any statistical confidence. The decision to include all AEDs also reflected

the general belief that more data was needed prior to making any more specific comments on the medications risks. It is also very important to note that the committees felt very strongly that the data do not warrant a black-box warning on any of the medication labels at this point. Contrary to the claims of Drs. Trimble and Kruszewski that it should have been obvious that gabapentin and similar drugs would lead to a worsening in mood and suicidality, it is important to note that members of the committee were admittedly surprised to find any association between AEDs and suicidality. This is reflected by the comments of Dr. Pine directed to the FDA representatives, stating "I think all of us would probably say that we were surprised to see the finding and it sounds like you guys were surprised as well and I think that reflects the fact that it's not an association that is frequently thought about."

In summary, the FDA analysis does provide strong evidence to suggest that some drugs with anticonvulsant properties are associated with an increased risk of suicidality. However, the analysis does not provide any credible evidence to suggest that gabapentin itself is associated with increased rates of suicidality.

In relation to the specific cases of Mr. Smith and Mr. Bulger, I do not see any scientific evidence in either the pharmacological mechanism of Neurontin (gabapentin) nor in the FDA's statistical analysis and review of AEDs as a class, or Neurontin in particular, to suggest that Neurontin would specifically be related to their suicides, nor that the scientific information available at the time of their deaths would have warranted any additional, different, or more specific testing or warnings regarding the risk of suicide that these lawsuits allege to be associated with Neurontin administration. In my opinion, for the reasons above and as outlined in my general causation report, there is no

credible scientific basis for those claims.

References

1. Taylor CP, Gee NS, Su TZ, Kocsis JD, Welty DF, Brown JP, et al. (1998): A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res.* 29:233-249.
2. Ng GY, Bertrand S, Sullivan R, Ethier N, Wang J, Yergey J, et al. (2001): Gamma-aminobutyric acid type B receptors with specific heterodimer composition and postsynaptic actions in hippocampal neurons are targets of anticonvulsant gabapentin action. *Mol Pharmacol.* 59:144-152.
3. Jensen AA, Mosbacher J, Elg S, Lingenhoehl K, Lohmann T, Johansen TN, et al. (2002): The anticonvulsant gabapentin (neurontin) does not act through gamma-aminobutyric acid-B receptors. *Mol Pharmacol.* 61:1377-1384.
4. Lanneau C, Green A, Hirst WD, Wise A, Brown JT, Donnier E, et al. (2001): Gabapentin is not a GABAB receptor agonist. *Neuropharmacology.* 41:965-975.
5. Maneuf YP, Gonzalez MI, Sutton KS, Chung FZ, Pinnock RD, Lee K (2003): Cellular and molecular action of the putative GABA-mimetic, gabapentin. *Cell Mol Life Sci.* 60:742-750.
6. Kelly KM (1998): Gabapentin. Antiepileptic mechanism of action. *Neuropsychobiology.* 38:139-144.
7. Goldlust A, Su TZ, Welty DF, Taylor CP, Oxender DL (1995): Effects of anticonvulsant drug gabapentin on the enzymes in metabolic pathways of glutamate and GABA. *Epilepsy Res.* 22:1-11.
8. Hendrich J, Van Minh AT, Heblich F, Nieto-Rostro M, Watschinger K, Striessnig J, et al. (2008): Pharmacological disruption of calcium channel trafficking by the alpha2delta ligand gabapentin. *Proc Natl Acad Sci U S A.* 105:3628-3633.
9. Petroff OA, Rothman DL, Behar KL, Lamoureux D, Mattson RH (1996): The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. *Ann Neurol.* 39:95-99.
10. Kuzniecky R, Ho S, Pan J, Martin R, Gilliam F, Faught E, et al. (2002): Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults. *Neurology.* 58:368-372.
11. Timmerman W, Bouma M, De Vries JB, Davis M, Westerink BH (2000): A microdialysis study on the mechanism of action of gabapentin. *Eur J Pharmacol.* 398:53-57.
12. Streeter CC, Jensen JE, Perlmutter RM, Cabral HJ, Tian H, Terhune DB, et al. (2007): Yoga Asana sessions increase brain GABA levels: a pilot study. *J Altern Complement Med.* 13:419-426.
13. Mason G, Watzl J, Gomez R, Krystal J, Rothman D, Sanacora G (2006): Effects of light deprivation on brain GABA and glutamate in healthy and depressed individuals. *Neuropsychopharmacology.* 31 S160-S160
14. Sanacora G, Saricicek A (2007): GABAergic contributions to the pathophysiology of depression and the mechanism of antidepressant action. *CNS Neurol Disord Drug Targets.* 6:127-140.
15. Sanacora G, Mason GF, Rothman DL, Behar KL, Hyder F, Petroff OA, et al. (1999): Reduced cortical gamma-aminobutyric acid levels in depressed patients

determined by proton magnetic resonance spectroscopy. *Archives of General Psychiatry*. 56:1043-1047.
16. Bhagwagar Z, Wylezinska M, Jezzard P, Evans J, Ashworth F, Sule A, et al. (2007): Reduction in Occipital Cortex gamma-Aminobutyric Acid Concentrations in Medication-free Recovered Unipolar Depressed and Bipolar Subjects. *Biol Psychiatry*.
17. Bhagwagar Z, Wylezinska M, Taylor M, Jezzard P, Watthews PM, Cowen PJ (2004): Increased brain GABA concentrations following acute administration of a selective serotonin reuptake inhibitor. *Am J Psychiatry*. 161.
18. Sanacora G, Mason GF, Rothman DL, Krystal JH (2002): Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *American Journal of Psychiatry*. 159:663-665.
19. Sanacora G, Mason GF, Rothman DL, Ciarcia JJ, Ostroff RB, Krystal JH (2003): Increased occipital cortex GABA concentrations following electroconvulsive therapy in depressed patients. *American Journal of Psychiatry*. 160:577-579.
20. Sanacora G, Gueorguieva R, Epperson CN, Wu Y-T, Appel M, Rothman DL, et al. (2004): Subtype-specific alterations of GABA and glutamate in major depression. *Archives of General Psychiatry*. 61:705-713.
21. Streeter CC, Hennen J, Ke Y, Jensen JE, Sarid-Segal O, Nassar LE, et al. (2005): Prefrontal GABA levels in cocaine-dependent subjects increase with pramipexole and venlafaxine treatment. *Psychopharmacology (Berl)*.1-11.
22. Goddard AW, Mason GF, Almai A, Rothman DL, Behar KL, Petroff OA, et al. (2001): Reductions in occipital cortex GABA levels in panic disorder detected with 1h-magnetic resonance spectroscopy. *Archives of General Psychiatry*. 58:556-561.
23. Dimond KR, Pande AC, Lamoreaux L, Pierce MW (1996): Effect of gabapentin (Neurontin) [corrected] on mood and well-being in patients with epilepsy. *Prog Neuropsychopharmacol Biol Psychiatry*. 20:407-417.
24. Perugi G, Toni C, Frare F, Ruffolo G, Moretti L, Torti C, et al. (2002): Effectiveness of adjunctive gabapentin in resistant bipolar disorder: is it due to anxious-alcohol abuse comorbidity? *J Clin Psychopharmacol*. 22:584-591.
25. Shiah I, Yatham LN (1998): GABA function in mood disorders: An update and critical review. *Life Sciences*. 63:1289-1303.
26. Sanacora G, Mason GF, Krystal JH (2000): Impairment of GABAergic Function in Depression: New Insights from Neuroimaging. *Critical Reviews of Neurobiology*. 14:23-45.
27. Brambilla P, Perez J, Barale F, Schettini G, Soares JC (2003): GABAergic dysfunction in mood disorders. *Molecular Psychiatry*. 8:721-737.
28. Tunnicliff G, Malatynska E (2003): Central GABAergic systems and depressive illness. *Neurochemical Research*. 28:965-976.
29. Schechter LE, Ring RH, Beyer CE, Hughes ZA, Khawaja X, Malberg JE, et al. (2005): Innovative approaches for the development of antidepressant drugs: current and future strategies. *NeuroRx*. 2:590-611.
30. Chang L, Cloak CC, Ernst T (2003): Magnetic resonance spectroscopy studies of GABA in neuropsychiatric disorders. *J Clin Psychiatry*. 64 Suppl 3:7-14.
31. Kasper S, Olie JP (2002): A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. *Eur Psychiatry*. 17 Suppl 3:331-340.

32. McEwen BS, Olie JP (2005): Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. *Mol Psychiatry*. 10:525-537.
33. Wilde MI, Benfield P (1995): Tianeptine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs*. 49:411-439.
34. Ruhe HG, Mason NS, Schene AH (2007): Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatry*. 12:331-359.

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